When the comparator has a confidential price

A review of recent cases in Sweden

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Background

Managed entry agreements (MEAs) are used in Sweden and elsewhere to facilitate market access for new pharmacological treatments when the traditional reimbursement pathway is unfeasible due to large uncertainties in costs or effects. They typically consist of risk sharing agreements that include confidential refunds. For prescription drugs, that pass the Swedish Dental and Pharmaceutical Benefits Agency (TLV) reimbursement route, MEAs are arranged through three-party deliberations between the manufacturer, TLV and representatives of the 21 regions that are responsible for financing and distribution of health care. In these situations, TLV is informed about the confidential net price. However, in the case of a hospital drug, TLV is consulted for the health economic appraisal, but the MEA is arranged between the manufacturers and the regions in a national tender process, without sharing information to TLV about the economical arrangements. MEAs are causing complications for new drug assessments, where drugs with a confidential price may be used as comparators.

Objectives

As new pharmacological treatments enter the market, using drugs with a confidential price as a comparator in the decision problem of the cost-effectiveness analysis has been proven difficult. The aim of this study is to provide an overview of how this situation is dealt with by TLV in prescription drug assessments.

Methods

Cases where the relevant comparator to the new drug was a drug with a confidential price were identified through a review of TLV prescription drug decisions through the TLV.se website. The review included all positive TLV decisions published between January 2016 and August 2019 and all decisions where the clinically relevant comparator was a drug for which a MEA with confidential pricing (e.g. in the form of refunds to the payers) were included. Drugs that were part of a group assessment (i.e. a multiple technical appraisal) were excluded.

Results

217 TLV decisions were reviewed, and seven met the inclusion criteria (Table 1). Mektovi and Braftovi are used in combination and are handled below as a single case.

Table 1. TLV decisions that met the inclusion criteria

Drug	Therapeutic area	Month for decision	Clinically relevant comparator	Alternative comparator requested
Verzenios (abemaciclib)	Breast cancer	June-19	Ibrance (palbociclib) or Kisqali (ribociclib)	Aromatase inhibitors (AI)
Mektovi (binimetinib) +Braftovi (encorafenib)	Malignant melanoma	Mar-19	Mekinist (trametinib) +Tafinlar (dabrafenib)	Tafinlar (dabrafenib)
Mekinist (trametinib)	Malignant melanoma	Mar-19	Standard of care or Opdivo (nivolumab) or Keytruda (pembrolizumab)	Standard of care
Ninlaro (ixazomib)	Multiple myeloma	May-18	Revlimid (lenalidomide) + dexamethasone	Revlimid (lenalidomide)+ dexamethasone
Cabometyx (cabozantinib)	Renal cell cancer	Mar-18	Opdivo (nivolumab) or Afinitor (everolimus)	Afinitor (everolimus)
Kisqali (trametinib)	Breast cancer	Jan-18	Ibrance (palbociclib)	Aromatase inhibitors (AI)

TLV assessments of the included cases are briefly described in Box 1-6 below.

Box 1: Verzenios

- Verzenios + aromatase inhibitor (AI) or fulvestrant (FUL) for the treatment of hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) breast cancer
- Relevant comparators are Ibrance and Kisqali
- The efficacy of Ibrance, Kisqali and Verzenios is comparable both in combination with AI and FUL
- Ibrance and Kisqali have confidential prices due to risk sharing agreements based off three-party deliberations, net prices known to TLV
- A risk sharing agreement was arranged also for Verzenios
- A cost comparison was made for Verzenios + AI vs Kisqali + AI based on the common comparator (AI monotherapy), applying the net costs for Verzenios and Kisqali.

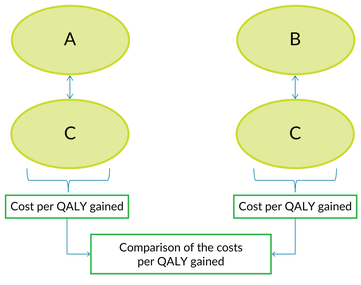
Box 2: Mektovi + Braftovi

- Mektovi + Braftovi for the treatment of malignant melanoma with BRAF V600-mutation.
- The clinically relevant comparator to Mektovi + Braftovi is Mekinist + Tafinlar.
- The efficacy of Mektovi + Braftovi is comparable to that of Mekinist + Tafinlar
- The Mekinist + Tafinlar combination was previously compared to Tafinlar monotherapy
- Mekinist has a confidential price due to a risk sharing agreement based off three-party deliberations, net price known to TLV
- Mektovi + Braftovi has not been compared to Tafinlar monotherapy in a clinical trial. TLV used Zelboraf (vemurafenib) as a proxy.
- TLV adjusted assumptions in the Mektovi + Braftovi model so that the gain in quality adjusted life years (QALYs) was equal to that of Mekinist + Tafinlar. Therefore, any differences in cost/QALY are mainly due to differences in costs (Figure 1).

Box 3: Mekinist

- Mekinist in combination with Tafinlar for the adjuvant treatment of malignant melanoma
- A risk sharing agreement was already in place for Mekinist
- Relevant comparators were standard of care, but also the programmed cell death protein-1 (PD-1)-inhibitors Opdivo and Keytruda
- Opdivo and Keytruda are hospital drugs and have confidential prices due to national tender, net prices not known to TLV
- TLV was therefore unable to perform a just comparison vs Opdivo and Keytruda
- Instead, TLV based the decision on a comparison vs observation

Figure 1. TLV method when the clinically relevant comparator to a new drug is a drug with a confidential price known to the agency



Box 4: Ninlaro

- Ninlaro in combination with Revlimid (lenalidomide) and dexamethason for treatment of multiple myeloma with at least two prior treatments
- Relevant comparator was Revlimid and dexamethason
- Revlimid has a confidential price due to a risk sharing agreement based off three-party deliberations, net price known to TLV
- A risk sharing agreement was arranged also for Ninlaro
- As Ninlaro is used as add-on to Revlimid, the comparator with confidential price is present in both arms in the model.
- TLV presented the Cost/QALY for Ninlaro + Revlimid + dexametason vs Revlimid + dexametason for different scenarios with hypothetical rebates for Revlimid.
- Without applying the rebate for Ninlaro in the model, the cost/QALY was slightly above the acceptable threshold.
- The cost/QALY for the Ninlaro combination was reduced with increasing rebates for Revlimid

Box 5: Cabometyx

- Cabometyx for the treatment of renal cell carcinoma
- The clinically relevant comparator is Opdivo
- Cabometyx and Opdivo has comparable efficacy
- A risk sharing agreement was arranged for Cabometyx
- Opdivo is a hospital drug and has a confidential price due to a national tender, net price not known to TLV
- TLV was therefore unable to perform a just comparison vs Opdivo
- Instead, TLV chose to compare Cabometyx with Afinitor in a cost utility analysis.

Box 6: Kisqali

- Kisqali (ribociclib) + an aromatase inhibitor (AI) for the treatment of HR+/HER2- breast cancer
- Relevant comparator is Ibrance (palbociclib) + AI
- The efficacy of Kisqali + AI and Ibrance + AI is comparable
- Ibrance has a confidential price due to a risk sharing agreement based off three-party deliberations, net price known to TLV
- A risk sharing agreement was arranged also for Kisqali
- A cost comparison was made for Kisqali + AI vs Ibrance + AI based on the common comparator (AI monotherapy), applying the net costs for Kisqali and Ibrance.

Discussions

- In the decisions reviewed, the confidential price of the clinically relevant comparator was unknown to TLV in the Mekinist and Cabometyx cases. In both cases, TLV based the decision on a cost utility analysis vs a different comparator.
- The net price of the comparators was known to TLV in four cases: Verzenios, Mektovi/Braftovi, Ninlaro and Kisqali.
- In the case of Ninlaro, the comparator was present in both arms of the model as Ninlaro is an add-on treatment. TLV circumvented the disclosure of net costs for the comparator by showing that even with relatively small hypothetical rebates for the comparator, the cost per QALY for Ninlaro could be assumed to fall under the willingness-to-pay threshold.
- For Verzenios, Mektovi/Braftovi and Kisqali, comparisons were carried out vs the common comparator with the clinically relevant one (in the case of Mektovi/Braftovi a proxy was used). TLV adjusted the model assumptions in order to resemble the comparator models as closely as possible and applied the confidential net price. A comparison of costs per QALY gained vs the clinically relevant comparators was the basis of the decision.

Conclusions

- In several cases where the clinically relevant comparator to a new drug (drug B) is a drug with a confidential price (drug A), TLV have instead requested a different comparator in the cost effectiveness model (drug C). This comparator can be identical to the comparator to drug A in its original reimbursement application, or a proxy, i.e. a drug with similar treatment effect. The cost effectiveness of drug B to drug A in thereafter assessed indirectly by comparing the cost per QALY gained for drug B vs drug C with that for drug A vs drug C (Figure 1). TLV justified this method with not being able to disclose the confidential price of drug B to the manufacturer of drug A.
- TLV has chosen different ways of handling this situation when (a) the confidential net price of the comparator is not known to TLV (e.g. when it has been subject of national tender rather than gone through the TLV reimbursement process for prescribed drug) and (b) when the new drug is an add-on treatment to the comparator.
- TLVs procedure of handling reimbursement applications when the clinically relevant comparator to a new drug has a confidential price is logical. However, the procedure causes issues for the manufacturers as the health economic model in Sweden will differ from other markets where authorities have other ways of handling this situation.

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